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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,337	04/25/2005	Yoshiaki Kawashima	12480-000063/US	5676

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EXAMINER	
HELM, CARALYNNE E	
ART UNIT	PAPER NUMBER
1615	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,337	KAWASHIMA ET AL.	
	Examiner	Art Unit	
	CARALYNNE HELM	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 08, 16 January 09 , 23 April 09* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-21,23-30,37-42,45 and 53-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-21,23-30,37-42,45 and 53-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/12/08, 7/10/08, 12/19/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election **without** traverse of Group I in the reply filed on January 4, 2008 is acknowledged. The claims drawn to the nonelected invention were cancelled by the applicant. The restriction is deemed proper and thereby made FINAL.

Claim Objections

Claim 53 and 64 are objected to because of the following informalities: line 3 of claim 64 contains the word "combing" which appears to be a misspelling of "combining". Claim 53 contains the terms "directing" and "directs" in a context that is unclear. These terms are interpreted as 'facing" and faces", respectively, which makes more sense in the context of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The four factual inquires of Graham v. John Deere Co. have been fully considered and analyzed in the rejections that follow.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-11, 13-15 and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trofast et al. (previously cited) in view of Dickinson et al. (WO 01/78689)

Trofast et al. teach a method of agglomerating fine drug particles via a dry process such that the agglomerated particles (composite particles) would be able to break up into their substituent particles during inhalation (page 2 lines 10-21, page 4 lines 7-8, page 5 lines 6-9; instant claim 10). In addition, they teach that finely divided particles (those less than 10 μm in diameter) are difficult to handle and meter, but their

agglomeration method alleviates these issues (see page 1 lines 15-21). Additionally, Trofast et al. teach that the agglomerates (primary particles) can be subjected to a secondary granulation process (see page 11 line 13- page 12 line 2 and page 12 lines 16-17 and figure 5; instant claims 13 and 38). Trofast also teaches that a binder (dry or liquid) can be used in their agglomeration process as well as additional ingredients other than the drug (see page 2 lines 10-14 and page 4 lines 26-30; instant claims 15-16 and 39). Further, Trofast et al. teach that the agglomeration process is performed by systematic agitation (fluid bed dry granulation) of powdered material to be formed into agglomerates (see page 2 lines 10-14; instant claims 15 and 39). An embodiment is taught where the agglomerates are formed by dry combination/granulation and then sent through a second dry combination/granulation process (see page 9 line 27-page 10 line 4; instant claim 10). The size of the agglomerates (primary particles) is a parameter that would depend on the particular processing equipment and other manufacturing conditions whose optimization would have been well within the purview of one of ordinary skill in the art at the time the invention was made (see instant claim 14). Trofast et al. do not specifically teach that the fine drug particles are less than 1000nm.

Dickinson et al. teaches a nanoparticle drug preparation intended for inhalation that are sized less than 1000 nm (see page 2 lines 22-26 and 33; instant claim 10). Since Trofast et al. teach the difficulty in metering and handling particulate preparations of this size, it would have been obvious to one of ordinary skill in the art at the time of the invention to use the nanoparticles of Dickinson et al. as the starting material in the method of Trofast et al. to prepare a reversibly collected drug composition for inhalation.

Therefore claims 10-11, 13-15 and 38-39 are obvious over Trofast et al. in view of Dickinson et al.

Claims 10-12 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trofast et al. in view of Kawashima (Advanced Drug Delivery Reviews 2001 47:1-2) and as evidenced by Dickinson et al.

Trofast et al. teach a method of agglomerating fine drug particles via a dry process such that the agglomerated particles (composite particles) would be able to break up into their substituent particles during inhalation (page 2 lines 10-21, page 4 lines 7-8, page 5 lines 6-9; instant claims 10 and 11). In addition, they teach that finely divided particles (those less than 10 μm in diameter) are difficult to handle and meter (see page 1 lines 15-21). An embodiment is taught where the agglomerates are formed by dry combination/granulation and then sent through a second dry combination/granulation process (see page 9 line 27-page 10 line 4; instant claim 10). Trofast et al, do not explicitly teach that the particles are less than 1000 nm or that they are made by spherical crystallization.

Kawashima teaches drug nanoparticles as improved drug delivery configurations due to their small size (see page 1 column 1 paragraphs 1 and 2). He goes on to teach several methods for making such particles, including spherical crystallization (see page 1 column 2 paragraph 2; instant claims 12 and 37). Since Dickinson et al. teach that nanoparticles are from 1 nm to 1000 nm in diameter, the nanoparticles of Kawashima are interpreted to be less than 1000 nm (see page 1 lines 10-11).

Since Trofast et al. teach the difficulty in metering and handling particulate preparations of this size, it would have been obvious to one of ordinary skill in the art at the time of the invention to use the nanoparticles of Kawashima as the starting material in the method of Trofast et al. so as to yield a more easily handled preparation. Therefore claims 10-12 and 37 are obvious over Trofast et al. in view of Kawashima and as evidenced by Dickinson et al.

Claims 10 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trofast et al. in view of Dickinson et al. as applied to claims 10-11, 13-15 and 38-39 above, and further in view of Nakagami et al. (US Patent No. 6,335,036).

Trofast et al. in view of Dickinson et al. make obvious the method of instant claim 15. This modified reference does not explicitly teach a biocompatible polymer in an aqueous solution as the binder.

Nakagami et al. teach the formation of medicinal agglomerates using granulation techniques. In particular polymers are envisioned as the binder and employed in an aqueous solution form (see column 2 lines 36-43 and column 3 lines 4-14; instant claim 16). Since the aqueous polymer binders of Nakagami et al. were known options at the time of the invention that would yield a predictable result, any one of them would have been an obvious selection to one of ordinary skill in the art for the liquid binder that can be included in the method of Trofast et al. Therefore claims 10 and 15-16 are obvious over Trofast et al. in view of Dickinson et al. and Nakagami et al.

Claims 10-11, 17-19, 40-41, 59-61 and 63-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishizaka et al. (previously cited) in view of Trofast et al. and Jain et al. (previously cited).

Ishizaka et al. teach a composite particle made by the combination of a drug powder and a core particle powder by mechanical impact (see column 4 lines 25-29, column 6 lines 3-5 and 12, and column 7 lines 37-42; instant claim 17 and 63-64). Ishizaka et al. go on to teach that starch or polyethylene glycol (biocompatible polymer), as the parent or core particle, ranges in size from 0.5μm to 1mm and that the child particles(drug) that are fixed to the surface are smaller in size (see column 3 lines 57-58 and column 4 lines 40-47; instant claims 18-19, 40-41, 59 and 61).

Jain et al. teach that drug particles sized less than 1000 nm were known in the art at the time of the invention for use in solid dosage forms due to their improved dissolution profile (see column 2 line 51-column 3 line 2 – implies step of making into nano particles; instant claims 10 and 59).

Trofast et al. teach a method of agglomerating fine drug particles via a dry process such that the agglomerated particles would be able to later break up (page 2 lines 10-21, page 4 lines 7-8, page 5 lines 6-9; instant claim 10). In addition, they teach that finely divided particles (those less than 10 μm in diameter) are difficult to handle and meter (see page 1 lines 15-21).

One of ordinary skill in the art would have found it obvious to use drug particles in nanoparticle size for their improved dissolution in the drug particles of Ishizaka et al. However, since Trofast et al. teach that such particulates are difficult to handle, it would

have further been obvious to subject these nanoparticles to agglomeration as taught by Trofast et al. and make a more easily handled, nanoparticle containing drug material for Ishizaka et al. Thus, when the size of the starch carrier particles of Ishizaka et al. is in the lower end of the range (e.g. 0.5μm) the drug particles (nanoparticle agglomerates) are less than 500nm in size (see instant claim 18). Since the particles agglomerates of Trofast et al. are reversibly collected, the composite itself is a reversible collection. As optimization of the sizing of the various particles and agglomerates would have been well within the purview of one of ordinary skill in the at the time of the invention, claims 10-11, 17-19, 40-41, 59-61 and 63-64 are obvious over Ishikawa et al. in view of Trofast et al. and Jain et al.

Claims 10, 17, 18, 20-21, 42, 59, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa et al. in view of Trofast et al. and Jain et al. as applied to claims 10, 17-19, 40-41, 59-61 and 63-64 above, and further in view of Bruno et al. (previously cited).

Ishizaka et al. in view of Trofast et al. and Jain et al. make obvious the limitations of claims 10, 17, 18, and 59. Here the polyethylene glycol is interpreted as a lubricant. This modified reference does not teach surface modification of the carrier using other particles.

Bruno et al. teach that milling is used to modify the surface properties to improve the dissolution properties of particles used in pharmaceuticals (see column 1 lines 9-14). Further Bruno et al. teach using other particles that are often used as lubricants

(e.g. copolymers of lactide and glycolide) to mill (modify the surface) the particles used in pharmaceutical preparations (see column 1 lines 61-64 and column 2 lines 48, 52, and 12-14; instant claims 20-21 and 42). It would have been obvious to one of ordinary skill in the art to use the milling method of Bruno et al. on the polymer particles to improve the dissolution properties of the composite particle made by the method of Ishizaka et al. modified by Trofast et al and Jain et al. Therefore claims 10, 17, 18, 20-21, 42, 59, and 62 are obvious over Ishizaka et al. in view of Trofast et al., Jain et al., and Bruno et al.

Claims 10 and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa et al. in view of Trofast et al. and Jain et al. as applied to claims 10, 17-19, 40-41, 59-61 and 63-64 above, and further in view of Hosokawa et al. (US Patent No. 4,789,105).

Ishizaka et al. in view of Trofast et al. and Jain et al. make obvious the limitations of claim 10, but do not explicitly teach the machinery of claim 53.

Hosokawa et al. teach an apparatus as well as its method of use for granulating (agglomerating) powdered materials (see abstract). In particular, the device allows for the combination of powdered materials via mechanical impact (see column 1 lines 6-18). The device is taught to have a cylindrical rotator with a receiving face and press head all housed within a casing (see column 4 lines 19-24 and 33-38; instant claim 53). The press heads press the material to be treated to the receiving face of the casing to combine particles with one another (see column 4 lines 33-45; instant claim 53). The

press heads themselves are depicted as semicircular with a curvature greater than that of the receiving face (see figures 6 and 14; instant claims 54-55). Hosokawa et al. go on to teach the apparatus for the coating of particles with other more fine particles where particles can range from 0.001-5 microns and 1-50 microns (see column 12 line 63-column 13 line 6).

The apparatus of Hosokawa et al. was known at the time of the invention as a means by which to mechanically combine particles into composite particles and had starting materials that were in the size range envisioned by Ishizaka et al. in view of Trofast et al. and Jain et al. Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to use the apparatus of Hosokawa et al. to produce the mechanically combined composite particles of Ishizaka et al. in view of Trofast et al. and Jain et al. as a known option within their technical grasp. Therefore claims 10 and 53-55 are obvious over Ishizaka et al. in view of Trofast et al., Jain et al. and Hosokawa et al.

Claims 23-27, 30, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishizaka et al. in view of Jain et al. reference B (US Patent No. 6,316,029), and Ryde et al.

Ishizaka et al. teach a dry method of making a composite particle with a drug containing parent or core particle (described as product A by reference), which ranges in size from 0.5μm to 1mm, and smaller child biocompatible polymer particles that are fixed to the surface (see column 3 lines 57-58, column 4 lines 40-47, and column 6 lines

3-5 and 12-13, column 7 lines 8-15; instant claim 23). Polyethylene glycol, starch, and hydroxypropyl cellulose are taught as envisioned polymers within the invention (see column 3 lines 46-53). This reference does not explicitly teach that the polymer is a lubricant.

Ryde et al. teach the production of a composite pharmaceutical where a surface stabilizer is adsorbed to the surface of a drug and both are sized such that the composite is less than about 1μm in size (e.g. both the drug and surface stabilizer are less than 1μm in size) (see column 6 lines 24-33 and column 7 lines 32-34; instant claims 23, 24, 30, and 45). Mechanical means are taught for adhering the stabilizer to the particle surface (see column 9 lines 34-35). A variety of materials are taught by Ryde et al. as surface stabilizers including hydroxypropyl cellulose and starch (see column 7 lines 40-43).

Jain et al. reference B teaches the production of a nanoscale composite pharmaceutical where a surface modifier (lubricant) is adsorbed to the surface of a drug (see column 5 lines 44-64 and column 6 lines 29-32; instant claims 23 and 24). These surface materials include polyethylene glycol, glycerol monostearate (sugar ester), colloidal silicon dioxide (colloidal silica), and hydroxypropylmethyl cellulose phthalate (see column 7 lines 34, 37, 45, and 49-50; instant claims 24-27 and 30).

Since Ishizaka et al., Ryde et al, and Jain et al. each teach functional equivalents for polymeric materials that are adsorbed to drug particles as surface modifiers, it would have been obvious to one of ordinary skill in the art to exchange the polyethylene glycol taught to by Ishizaka et al. for glycerol monostearate (sugar ester) or colloidal silicon

dioxide. Both Ryde et al. and Ishizaka et al. teach mechanical means for adhering the surface stabilizer polymer to the drug particle surface indicating that such a methodology was known at the time of the invention. Further, the teachings of Ishizaka et al. about the sizing of their composite particles, core particles and child particles would have equipped and made it obvious to one of ordinary skill in the art to size the drug particles at 500 μm and the polymer above or below 1000 nm. Therefore claims 23-27, 30, and 45 are obvious over Ishizaka et al. in view of Jain et al. and Ryde et al.

Claims 23-24, 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishizaka et al. in view of Jain et al. and Ryde et al. as applied to claims 23-27, 30, and 45 above, and further in view of Kawashima and Murakami et al. (Advanced Powder Technology 2000 11:311-322).

Ishizaka et al. in view of Jain et al. and Ryde et al. make obvious the claimed method of preparing composites of drug particles coated by biocompatible polymer particles where the polymer is also known as a pharmaceutical excipient. The modified reference does not explicitly teach nanoparticulate PLGA produced by spherical crystallization as the biocompatible polymer.

Kawashima teaches the production of poly(lactic acid-co-glycolic acid) copolymer (PLGA) containing nanoparticles by spherical crystallization (see page 1 column 2 paragraph 1).

Murakami et al. teach that PLGA nanoparticles were well known as pharmaceutical excipients (see page 213 paragraph 1). One of ordinary skill would have

found it obvious to apply this known component as a surface modifier in the invention of Ishizaka et al. in view of Jain et al. and Ryde et al. with a reasonable expectation of success. Since Kawashima teaches PLGA nanoparticles made by spherical crystallization, it also would have been obvious to employ this method as one of a finite number of options known at the time of the invention. Therefore claims Ishizaka et al. in view of Jain et al., Ryde et al., Kawashima, and Murakami et al.

Claims 23 and 56-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishizaka et al. in view of Jain et al. and Ryde et al. as applied to claims 23-27, 30, and 45 above, and further in view of Hosokawa et al.

Ishizaka et al. in view of Jain et al. and Ryde et al. make obvious the claimed method of preparing composites of drug particles coated by biocompatible polymer particles. This modified reference does not explicitly teach the use of the machinery of claim 56

Hosokawa et al. teach an apparatus as well as its method of use for granulating (agglomerating) powdered materials (see abstract). In particular, the device allows for the combination of powdered materials via mechanical impact (see column 1 lines 6-18). The device is taught to have a cylindrical rotator with a receiving face and press head all housed within a casing (see column 4 lines 19-24 and 33-38; instant claim 56). The press heads press the material to be treated to the receiving face of the casing to combine particles with one another (see column 4 lines 33-45; instant claim 56). The press heads themselves are depicted as semicircular with a curvature greater than that

of the receiving face (see figures 6 and 14; instant claims 57-58). Hosokawa et al. go on to teach the apparatus for the coating of particles with other more fine particles where particles can range from 0.001-5 microns and 1-50 microns (see column 12 line 63-column 13 line 6).

The apparatus of Hosokawa et al. was known at the time of the invention as a means by which to mechanically combine particles into composite particles such that fine particles coated larger particles and had starting materials that were in the size range envisioned by Ishizaka et al. in view of Ishizaka et al. in view of Jain et al. and Ryde et al. Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to use the apparatus of Hosokawa et al. to produce the mechanically combined composite particles of Ishizaka et al. in view of Trofast et al. and Jain et al. as a known option within their technical grasp. Therefore claims 10 and 53-56 are obvious over Ishizaka et al. in view of Jain et al., Ryde et al., and Hosokawa et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 23-24 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12 and 16 of U.S. Patent No. 7,022,311. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claim a dry process of making a composite particle with a drug and carrier/surface modifier/nano particle where the carrier is taught be less than 1000nm (see claim 17). It would have been obvious to one of ordinary skill in the art to use the teachings in claim 17 of Patent No. 7,022,311 to practice the method of claims 12 and 16. Therefore, instant claims 1 and 23-24 are obvious over claims 12 and 16 of U.S. Patent No. 7,022,311.

Claims 10 and 23-24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22, 31-34 of copending Application No. 12/068499. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite nearly identical methods of making composition particles. Instant claim 10 corresponds to claims 32 and 33 instant claim 23 to claims 22 and 31; and instant claim 24 corresponds to claim 34. Here the primary different between the claims of the instant application and those of copending Application No. 12/068499 is the recited intended

use in the copending application, Therefore claims 10 and 23-24 are obvious over claims 22, 31-34 of copending Application No. 12/068499.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicants' arguments, filed July 10, 2008 and August 8, 2008, have been fully considered but they are not deemed to be persuasive.

The arguments regarding each of the rejections under 35 U.S.C. 103(a) all discuss how each reference does not teach the combination of the drug particles into primary particles or that the primary particles should be reversible combined. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding rejection of claims 10-15 and 37-39 under 35 U.S.C. 103(a):

Applicant argues that Trofast, unlike the instant invention teaches a one step process and that Jain et al. does not cure this deficiency. Trofast does teach the reversible collection of particles less than 5μm in size into larger agglomerates. They further teach that the formed agglomerates are from 0.2 to 2 mm (see page 10 lines17-19). In addition to the single pass process that applicant highlights, Trofast et al. also

teach a method where the agglomerates are formed by dry a combination/granulation process that is then followed by a second dry combination/granulation process (see page 9 line 27-page 10 line 4). Thus Trofast et al. contemplated both an initial agglomeration of individual particles and the combination of multiple agglomerates into a larger composite. Further, Jain provides the teaching that drug particles less than 1000 nm, which also meet the size limitations taught by Trofast, were known for use in solid drug dosage forms for their improved dissolution profile. Nanoparticles were well known at the time of the invention to be particularly desirable in inhaled preparations and since such preparations were the subject of the Trofast invention, one of ordinary skill in the art would have been further motivated to employ them in the Trofast et al. method. Taken together, Trofast and Jain et al. make obvious the claimed two step method of making the drug composite particles.

Regarding rejection of claims 10, 17-19, and 40-41 under 35 U.S.C. 103(a):

As this is rejection based upon the combination of Ishizaka et al. with the teachings of Trofast and Jain et al., applicant's assertion that the references do not make obvious claim 10 are not persuasive. Instant claims 17-19 and 40-41 add limitations drawn to a carrier particle used in conjunction with the drug particles in the reversibly collected agglomerates. Trofast does provide teachings about other ingredients being incorporated with the drug particles (see page 5 lines 28-29). Ishizaka et al. then provide teachings about composite particles with drug particles on carrier particles. In particular, they teach carrier particles being used that are larger in size than

the drug particles they carry, as well as a type and particular size range of carrier particles that had been used (see column 3 lines 42-58 and column 4 lines 43-47). In view of these teachings, it would have been obvious to one of ordinary skill in the art to produce such a configuration using the method of Trofast in view of Jain et al. where carrier particles that are larger in size than the drug particles (primary particles) carry the drug on their surface. Further, such a process would also facilitate the use of nanoparticulate drug that is easy to handle due to its processing by the method of Trofast.

Regarding rejection of claims 10, 17-18, 20-21, and 42 under 35 U.S.C. 103(a):

Instant claims 20-21 and 42 add the step of altering the surface of the carrier particles by a dry mechanical process prior to its combination with the drug particles to the method recited in claims 10 and 17-18 that was addressed above. As discussed, Bruno et al. teach a method of preparing a finely divided drug particulate material by a dry grinding process and teach that the resulting material is less than 500 nm (see column 3 lines 50-54). As a known method of generating the nanoparticles, it would have been well within the technical grasp of one of ordinary skill in the art at the time of the invention to use this method to generate the starting drug material for the process of Ishikawa et al. in view of Trofast et al. and Jain et al.

Regarding rejection of claims 23-27, 30, and 45 under 35 U.S.C. 103(a):

Applicant argues that there is no suggestion to substitute drug core particles for the parent core particles taught by Ishizaka et al. The rejection highlights the example of Ishizaka et al. where a drug containing core particle is coated with polyethylene glycol particles by mechanical means. Thus Ishizaka et al. explicitly teaches a drug containing particle as a core particle in their invention (see column 7 lines 8-15).

Regarding Double Patenting rejection:

Applicant argues that since claim 4 of patent 7,022, 311 recites a surface modifier with an average size of 1.5 μm in the particle to be made by the recited method, that the limitations of instant claim 23 requiring a particle less than 1000 nm are not met. The claims of patent 7,022, 311 clearly envision particles that are below 1000 nm in size in the composite particle (e.g. claim 17). Routine experimentation by one of ordinary skill in the art base upon the claims of patent 7,022, 311 would have made the instant claims obvious.

Applicant further argues that claim 24 of patent 7,022, 311 does note explicitly teach or suggest a lubricant. However the claim is drawn to a surface modifier where trehalose is named. This was a well known lubricant in the pharmaceutical art and, although not described as a "lubricant" in patent 7,022, 311, still meets the limitations of a lubricant.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or

newly applied. They constitute the complete set presently being applied to the instant application.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CARALYNNE HELM whose telephone number is (571)270-3506. The examiner can normally be reached on Monday through Thursday 8-5 (EDT).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Caralynne Helm/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615